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Varicella-Related Hospitalizations in the United States, 2000 – 2006: The 1-Dose Varicella Vaccination Era

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Abstract

OBJECTIVE—To describe the effect of the mature 1-dose varicella vaccination program on varicella morbidity, we analyzed 2 national databases for varicella-related hospitalizations in the United States since implementation of the varicella vaccination program in 1995.

PATIENTS AND METHODS—Data from the National Hospital Discharge Survey and Nationwide Inpatient Sample were analyzed to describe trends in varicella-related hospitalizations during the 1-dose vaccination era (2000 –2006) compared with those in the prevaccination era (1988 –1995). Varicella-related hospitalizations were defined by using *International Classification of Diseases, Ninth Revision* codes. Results were extrapolated to represent national estimates.

RESULTS—Using National Hospital Discharge Survey data, 24 488 varicella-related hospitalizations were estimated to occur in the United States during the 1-dose vaccination era. The varicella-related hospitalization rate was 0.12 per 10 000 population during the 1-dose vaccination era versus 0.42 per 10 000 population in the prevaccination era ($P < .01$). During the 1-dose vaccination era, the estimated annual average number of varicella-related hospitalizations was significantly lower and decreased by ≥65% in all age groups compared with those in the prevaccination era ($P < .001$ in all age groups). The varicella-related hospitalization rate during the 1-dose vaccination era estimated from the Nationwide Inpatient Sample was 0.09 per 10 000 population.

CONCLUSIONS—Varicella-related hospitalization numbers and rates declined significantly during the 1-dose varicella vaccination era. Assuming declines in varicella-related hospitalizations are due, mainly, to the routine childhood varicella vaccination program, these data suggest that varicella vaccination prevented ~50 000 varicella-related hospitalizations in the United States from 2000 to 2006. *Pediatrics* 2011; 127:000

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Keywords

varicella-related hospitalizations; varicella vaccination; varicella-related hospitalization rates; United States; 1-dose varicella vaccination era

The varicella vaccination program, implemented in 1995, has decreased varicella incidence and mortality in the United States.[1–7] Data from active surveillance sites demonstrated a 90% decline in varicella from 1995 to 2005.[4] Data from passive surveillance from 4 states showed declines in varicella incidence ranging from 53% to 94% by 2005 compared with the prevaccination era.[8] In a number of studies that examined the early impact of the varicella vaccination program on varicella hospitalizations, evidence of decline after vaccine implementation was found,[2,6,9–13] although statistically significant declines were not reported in all studies.[9,10]

To further evaluate trends in varicella-related hospitalizations in the United States before the implementation of the routine 2-dose varicella vaccination program, we analyzed data from the National Hospital Discharge Survey (NHDS) from 1988 to 2006 and from the Nationwide Inpatient Sample (NIS) from 1998 to 2006 to calculate estimates of numbers and rates of varicella-related hospitalizations and to describe changes in the epidemiology of varicella-related hospitalizations after implementation of the varicella vaccination program.

PATIENTS AND METHODS

Data Sources

The NHDS is based on a nationally representative sample of inpatient discharge records from noninstitutional, nonfederal, short-stay hospitals. The NHDS has a 3-stage sampling design: stage 1 includes all US hospitals with 1000 or more beds; stage 2 includes a representative sample of other hospitals on the basis of size, specialty, and geographic location; and stage 3 includes a random sample of discharges from each of the hospitals. The discharge records are weighted according to hospital size and region to allow calculation of national estimates. From 1988 to 2006, NHDS collected data on hospitalizations from a nationally representative sample of ~500 hospitals that represent ~270 000 entries per year.[14]

The NIS, a component of the Healthcare Cost and Utilization Project, is sponsored by the Agency for Healthcare Research and Quality and is currently the largest inpatient care data set that is publicly available in the United States. The NIS is a nationally representative annual sample of discharges from all community hospitals, defined as nonfederal, short-term, general, and other specialty hospitals.[15] It is designed to approximate a 20% sample of US community hospitals stratified by hospital ownership/control, bed size, teaching status, urban/rural location, and US region. The NIS includes information on between 5 and 8 million discharges per year from ~1000 hospitals. Discharge level weights are used to calculate national estimates of hospital discharges.[15] We analyzed data from 1998, the first year when at least 20 states participated and the number of hospitals sampled neared 1000.

Study Definitions

The methodology for identifying varicella-related hospitalizations was the same as that described by Galil et al.[9] Varicella-related hospitalizations were defined by using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes (ICD-9) as follows: (1) varicella as the principal discharge code (052– 052.9); (2) postvaricella encephalitis (052.0) or varicella pneumonitis (052.1) in any diagnostic position; or (3) varicella in any diagnostic position in a person with a severe immunocompromising condition that would likely necessitate hospitalization for varicella [HIV infection, malignancy, severe defect of T cell immunity, organ transplant recipient, or chemotherapy recipient]; or (4) a well-described potential complication of varicella as the principal discharge diagnosis and a varicella code in any subsequent position. Fluid/electrolyte disturbances were defined by using ICD-9 codes for the following conditions: volume depletion; hyposmolality; hyponatremia; hyperpotassemia; hypopotassemia; or other electrolyte and fluid disorders. Hospitalizations with an ICD-9 code for varicella that did not meet the above criteria were defined as incidental cases of varicella (eg, hospitalization during a varicella infection for a reason other than the varicella or varicella infection with onset during hospitalization for another reason). To address the possibility that our reliance on electronic coding to identify varicella-related hospitalizations could have resulted in the inadvertent inclusion of incidental varicella hospitalizations, we also calculated varicella-related hospitalization rates by using a more restrictive case definition that was limited to hospitalizations in which varicella was listed as the principal discharge code. Hospitalizations with coexistent herpes zoster codes (053.xx) were excluded.

Patients were stratified by underlying health status into 3 mutually exclusive categories: (1) having no comorbid or immunocompromising condition; (2) having a comorbid condition (eg, diabetes or cardiac disease); or (3) immunocompromised (eg, HIV or cancer). Because NIS records include up to 15 diagnostic positions, we limited analysis to the first 7 ICD-9 codes to maintain comparability with the NHDS data, which only contain 7 diagnostic positions.

We defined the prevaccination era as 1988 –1995, the period before licensure and widespread use of the varicella vaccine. The 1-dose vaccination era was defined as the years 2000 to 2006, a period when 1-dose national varicella vaccination coverage was >65%[16] and before implementation of the universal 2-dose vaccination recommendation.

Data Analysis

The varicella-related hospitalization numbers and rates we present are extrapolations to represent national estimates. Data from the US Census and the National Health Interview Survey were used as the denominators to calculate varicella-related hospitalization rates per 10 000 population and per 10 000 varicella cases, respectively. Rates per 10 000 cases from the prevaccination era could not be compared with rates from the 1-dose vaccination era because of changes in methodology for collecting data on numbers of varicella cases in the National Health Interview Survey in 2000. Confidence intervals (CIs) for rates were calculated using the Taylor series linearization method to account for the complex survey designs.

SUDAAN 10.0 (SAS Institute, Inc, Cary, NC) was used for analysis. Poisson regression method was used as a test for trend. Analyses of varicella-related complications were limited by sample size; estimates on the basis of unweighted sample sizes of <30 are considered unreliable and not reported.

RESULTS

NHDS

Estimated Number of Varicella Hospitalizations—On the basis of NHDS data, an estimated 34 774 hospitalizations with a varicella discharge diagnosis were identified in the United States during the 1-dose vaccination era (2000– 2006). Of these, 3052 (8.8%) hospitalizations were excluded because of coexisting herpes zoster codes and 7234 (20.8%) as incidental varicella cases, leaving 24 488 (70.4%) varicella-related hospitalizations. This corresponds to an estimated annual average of 3498 varicella-related hospitalizations [95% CI: 2447– 4549] during the 1-dose vaccination era, compared with 10 632 during the prevaccination era ($P < .01$). The estimated number of varicella-related hospitalizations in the United States during the 1-dose vaccination era varied from a peak of 4809 in 2000 to a low of 1718 in 2006 ($P < .01$). Of the 24 488 varicella-related hospitalizations, 20 387 (83.2%) had varicella listed as the principal discharge code, which resulted in an average annual estimate of 2912 varicella-related hospitalizations, compared with an average annual estimate of 8680 during the prevaccination era, using this more restrictive definition ($P < .01$).

Rates of Varicella Hospitalizations—The overall varicella-related hospitalization rate on the basis of NHDS data was 0.12 (95% CI: 0.08–0.16) per 10 000 population during the 1-dose vaccination era versus 0.42 (95% CI: 0.33– 0.50) per 10 000 population in the prevaccination era ($P < .01$) (Fig 1). The overall varicella-related hospitalization rate per 10 000 varicella cases was 23.1 during the 1-dose vaccination era and fluctuated annually (Fig 1).

The estimated average annual varicella-related hospitalization rates on the basis of NHDS data decreased by >70% in all age groups younger than 20 and by 65% in the 20-and-older age group during the 1-dose vaccination era compared with the prevaccination era ($P < .001$ for trend) (Fig 2). Although rates remained highest for the youngest age group (0–4 years), they were 72% lower than during the prevaccination era ($P < .001$ for trend) (Table 1). The proportions of hospitalizations by age group did not differ substantially when varicella-related hospitalizations were limited to those with varicella listed as the principal discharge code.

Characteristics of Varicella-Related Hospitalizations (NHDS)

Age and Gender—The mean overall age of persons discharged after a varicella-related hospitalization in NHDS was 22 years (median: 10 years; range: 1 month to 84 years) during the 1-dose vaccination era compared with 14 years (median: 6 years; range: 1 day to 99 years) during the prevaccination era ($P < .01$). The proportion of varicella hospitalizations in persons younger than 10 years decreased over time (Table 1). A greater proportion of the

varicella-related hospitalization cases during the 1-dose versus prevaccination eras were male (65.6 vs 57.5%; $P < .01$). This difference was especially pronounced during the 1-dose vaccination era among persons aged 0 to 4 years (70.3% male) and 20 and older (69.6% male).

Underlying Conditions—The proportion of varicella-related hospitalizations with no comorbid or immunocompromising conditions was similar to that in the prevaccination era (70.0 vs 70.4%, respectively), whereas the proportion with immunocompromising conditions increased from 10.9% in the prevaccination era to 14.4% in the 1-dose vaccination era ($P < .01$) (Fig 3). The proportion of persons with a varicella-related hospitalization with ≥1 comorbid medical conditions decreased to 15.3% in the 1-dose vaccination era compared with 19.2% in the prevaccination era ($P < .01$).

Length of Hospitalization—The mean length of varicella-related hospitalization during the 1-dose vaccination era was 4.6 days (median: 4 days; range: 1–203 days), corresponding to 16 149 days of hospitalization annually. The mean length of hospitalization during the prevaccination era was 5.4 days (median: 4 days; range: 1–153 days), corresponding to 56 975 days of hospitalization annually. As in the prevaccination era, mean length of stay varied by health status: during the 1-dose vaccination era, persons with no comorbid or immunocompromising conditions had a mean stay of 3.2 days, compared with 6.3 days among persons with comorbid conditions ($P < .01$) and 9.5 days among persons with underlying immunocompromising conditions ($P < .01$).

Complications of Varicella—The numbers of varicella-related complications among varicella-related hospitalizations decreased from the prevaccination era such that the numbers are now too small to calculate reliable overall and age-specific rates for the 1-dose vaccination era. Slightly more than half (54.6%) of varicella-related hospitalization cases during the 1-dose vaccination era had ≥1 complication compared with 65.4% during the prevaccination era ($P < .01$). Fluid/electrolyte disturbances were the most frequently recorded varicella-related complication followed by pneumonias/lower respiratory infections in the 1-dose vaccination era. In contrast, pneumonias/ lower respiratory infections were the most frequently recorded varicella-related complication, followed by fluid/electrolyte disturbances in the prevaccination era. The mean age of varicella-related hospitalization cases with complications varied from 6.6 years among those with skin/soft tissue infections to 16.2 years among those with fluid/ electrolyte disturbances, and 18.9 years among those with pneumonia/respiratory infections.

NIS

Estimated Number of Varicella Hospitalizations—On the basis of NIS data, an estimated total of 27 543 hospitalizations with a varicella discharge diagnosis were identified in the United States during the 1-dose vaccination era. Of these, 1713 (6.2%) were excluded because of coexistent herpes zoster diagnoses and 7756 (28.2%) as incidental cases of varicella. The remaining 18 074 (65.6%) varicella-related hospitalizations correspond to an estimated annual average of 2582 [95% CI: 2223–2941]. This represents a 26.2% lower number of varicella-related hospitalizations during the 1-dose vaccination era compared with

estimates obtained from the NHDS data during the same period, a difference that was statistically significant. Of the 18 074 varicella-related hospitalizations estimated from NIS data, 14 951 (82.7%) had varicella listed as the principal discharge code, for an average annual estimate of 2136 varicella-related hospitalizations using the more restrictive definition.

Rates of Varicella Hospitalizations—The overall varicella-related hospitalization rate estimated by using NIS for the 1-dose vaccination era was 0.09 per 10 000 population and 17.0 per 10 000 varicella cases. The rates were 25.0% and 26.4% lower, respectively, than NHDS rates and were statistically significantly different. Similar to findings from the NHDS data, varicella-related hospitalization rates calculated using NIS data were highest among the 0 to 4 years age group but decreased by 70.1% when comparing 2000 with 2006 ($P < .001$). Rates for the 20-and-older age group also decreased, by 50% when comparing 2000 with 2006 ($P < .001$) (Fig 2).

DISCUSSION

During the 1-dose vaccination era (2000 –2006), varicella-related hospitalization rates estimated from the National Hospital Discharge Survey decreased significantly, by 71%. Our findings confirm and update trends first suggested by authors of earlier studies in which NHDS was used,[9,10] studies in which declines in varicella-related hospitalizations from 1996 to 1999 were reported. Varicella-related hospitalization rates continued to be highest in the 0 to 4 years age group but were 72% lower than during the prevaccination era; importantly, rates in the 20-and-older age group did not increase after introduction of varicella vaccination, and in fact declined 65% during the 1-dose varicella vaccination era. Assuming that declines in varicella-related hospitalizations are due, in large part, to the routine childhood varicella vaccination program, these data suggest that varicella vaccination prevented ~50 000 varicella-related hospitalizations in the United States from 2000 to 2006. In addition, the declines in varicella-related hospitalizations have translated to significant declines in the direct medical costs for varicella-related hospitalizations since introduction of the varicella vaccine in 1995.[2,5]

Although varicella-related hospitalization rates declined significantly from the prevaccination era, rates continued to be highest in the youngest age group (0–4 years). This is consistent with other studies in which the effect of varicella vaccination during prevaccine and postvaccine introduction has been examined.[2,6,17] Numbers were too small to estimate rates for the age group of children younger than 1, but overall declines in the 0 to 4 years age group likely included declines in the group of children younger than 1. Declines in the group of children younger than 1, for whom vaccination is not recommended, would be a result of herd immunity provided by the high vaccination coverage in older age groups. Ensuring high vaccination coverage among susceptible persons eligible for vaccination (eg, persons living with or caring for infants younger than 1) is important for protecting those who cannot be vaccinated because they are too young or have contraindications for vaccination.

Concerns have been raised that a universal childhood varicella vaccination program could shift varicella disease burden to older persons and result in more severe disease.[18,19] In this

study, varicella-related hospitalization numbers and rates have actually declined in all age groups, including the 10 to 19 and 20-and-older age groups. The mean age of persons hospitalized for varicella increased from the prevaccination to the 1-dose vaccination era, which is a result of the large decrease in incidence among younger age groups targeted for vaccination. Ensuring high varicella vaccination coverage among children and adolescents is critical for maintaining low rates of varicella-related hospitalizations while cohorts for whom varicella vaccination is recommended age into adulthood, when varicella disease can be more severe.[20–22] Varicella vaccination school entry requirements for middle school–, high school–, and college-aged persons can be an effective tool for achieving high coverage in these age groups.[1]

As the number of varicella-related hospitalizations decreases over time, varicella-related complications among hospitalized persons have become so rare that calculations of complication rates through NHDS are no longer reliable. Although rare, the bulk of varicella complications continue to occur among persons with no comorbid or immunocompromising conditions. Similar to findings from the prevaccination era,[20,21,23] the most frequently reported complications during the 1-dose vaccination era continued to be fluid/electrolyte disturbances, skin/ soft tissue infections, and lower respiratory infections (ie, pneumonias).

Varicella vaccination coverage in children aged 19 to 35 months reached 89% in 2006.[24] Despite coverage data being available only for this younger age group, we noted decreasing varicella-related hospitalization rates in all age groups during the 1-dose vaccination era. The number of varicella-related hospitalizations is expected to continue to decline with increasing vaccination coverage because varicella disease in vaccinated persons is generally milder than that among the unvaccinated, with fewer lesions and a shorter duration of illness.[25–27] Data from varicella active surveillance sites showed that during from 1995 to 2005, among persons with varicella, the rate of hospitalization was two-thirds lower among those who were vaccinated compared with those who had not been.[6] The data sources used in our study lack information on varicella vaccination status for the varicella-related hospitalization cases; thus we are unable to compare hospitalization rates between vaccinated and unvaccinated persons. Additional assessment of the effect of the varicella vaccination program on varicella-related hospitalizations should include monitoring of the extent to which hospitalizations are occurring among vaccinated persons.

Our study was subject to several limitations. First, results from analyses of hospital discharge codes must be interpreted with caution because diagnostic codes for varicella could have been misattributed or inadvertently excluded. It is possible that adults with herpes zoster could have been miscoded as varicella; to control for this, we excluded those hospitalizations with a coexistent herpes zoster code and analyzed the data by using a stricter definition limited to varicella-related hospitalizations with varicella listed as the primary diagnosis code. Second, hospital discharge data do not include enough clinical information to determine severity of disease and reason for hospitalization. It is possible that hospitalization varies by factors other than severity, such as age. Using hospitalizations to track changes in severity of varicella over time may be confounded by changing hospitalization practices. Finally, because the numbers of varicella-related hospitalizations declined greatly during the 1-dose vaccination era, we were limited in the analyses we could

perform using NHDS and could not estimate varicella-related hospitalization rates in children younger than 1 or age-specific rates of complications.

Analyses of varicella-related hospitalizations using both the NHDS and NIS allow us to show that comparable estimates are obtained using the different data sources. We were not able to validate varicella-related hospitalizations through examination of medical charts, but comparing results from both sources provided a form of validation. The difference between the varicella-related hospitalization rates per population from the NHDS and NIS translates to ~128 hospitalizations per year or 900 hospitalizations for the 1-dose vaccination era. Both data sources are designed to provide nationally representative estimates, so it is unlikely that the composition of the hospitals in each source is different enough to explain the differences in varicella-related hospitalization rates. Because the difference in estimates between the 2 surveys is significant, although the trend is similar, the estimates from the NIS, with its larger sample size, may be closer to the true estimate for varicella-related hospitalizations. As the number of varicella-related hospitalizations continues to decline, the NIS may be a better source for evaluating additional trends in varicella-related hospitalizations and complications.

CONCLUSIONS

Our analyses of hospital discharge data from the NHDS and NIS provide updates to previous analyses of varicella-related hospitalizations and show statistically significant declines in varicella-related hospitalizations during the 1-dose vaccination era. The most dramatic declines were noted in those age groups targeted for vaccination (<10 years of age), suggesting successful impact of the varicella vaccination program. Despite early concerns about a shift in age of varicella cases because of the vaccination program,[18,19] significant declines were also seen in varicella-related hospitalizations among the age group of persons aged 20 and older. In 2006, the Advisory Committee on Immunization Practices recommended implementation of a routine second dose of varicella vaccine for children with the first dose given at 12 to 15 months and the second dose at 4 to 6 years.[1] It is expected that the implementation of this recommendation will lead to additional declines in varicella incidence and hospitalization rates.

ABBREVIATIONS

NHDS	National Hospital Discharge Survey
NIS	Nationwide Inpatient Sample
ICD-9	*International Classification of Diseases, Ninth Revision*
CI	confidence interval

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WHAT'S KNOWN ON THIS SUBJECT

A number of studies have examined the early impact of the varicella vaccination program on varicella-related hospitalizations and have found evidence of decline after vaccine implementation.

WHAT THIS STUDY ADDS

This study further documents the continued decline in varicella-related hospitalizations during the 1-dose varicella vaccination era and demonstrates statistically significant declines of >65% in all age groups. These data suggest that varicella vaccination prevented ~50 000 hospitalizations from 2000 to 2006.

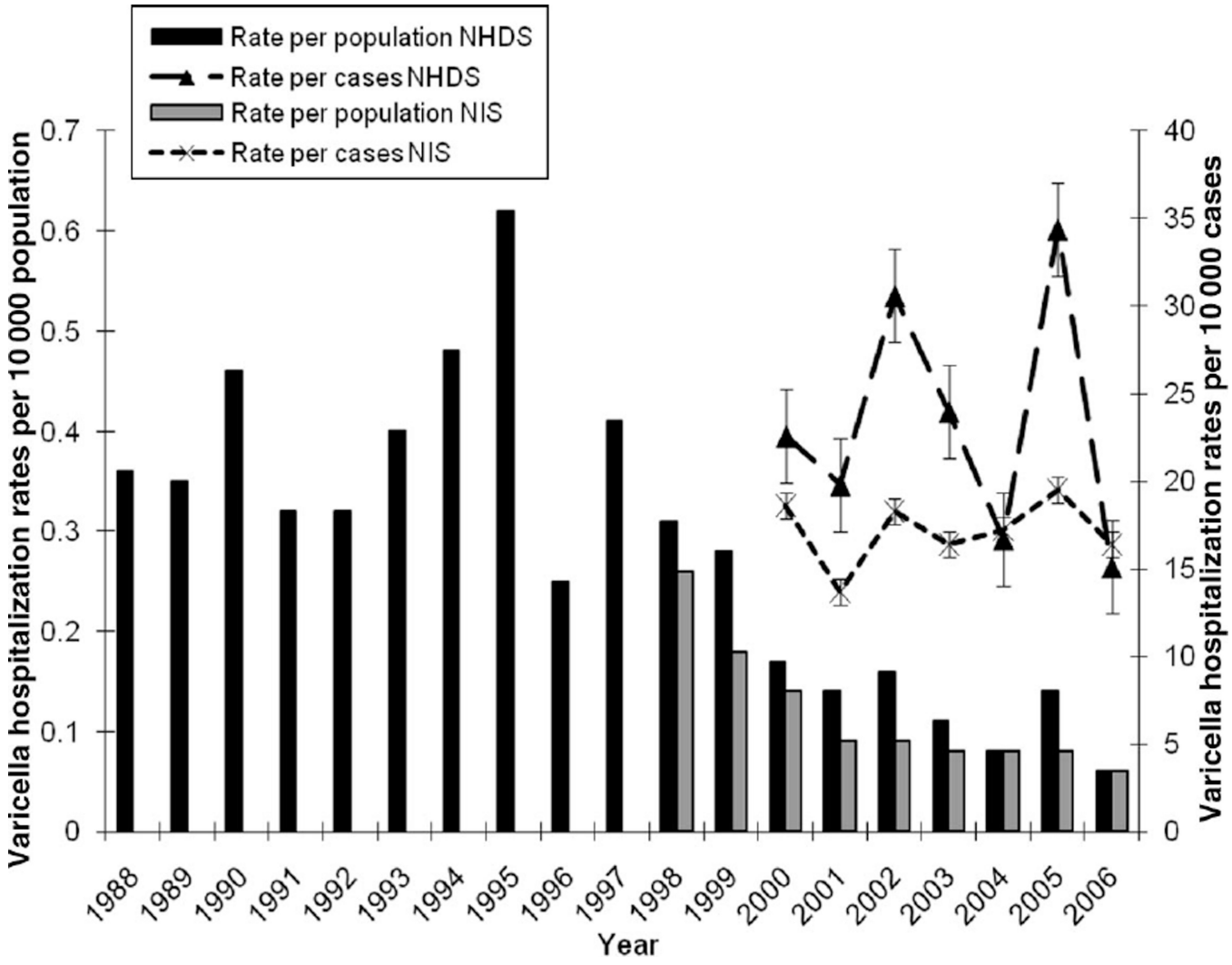

FIGURE 1.

Varicella-related US hospitalizations per 10 000 population from 1988 to 2006 and per 10 000 varicella cases from 2000 to 2006. Rates were estimated by using data from the NHDS and NIS.

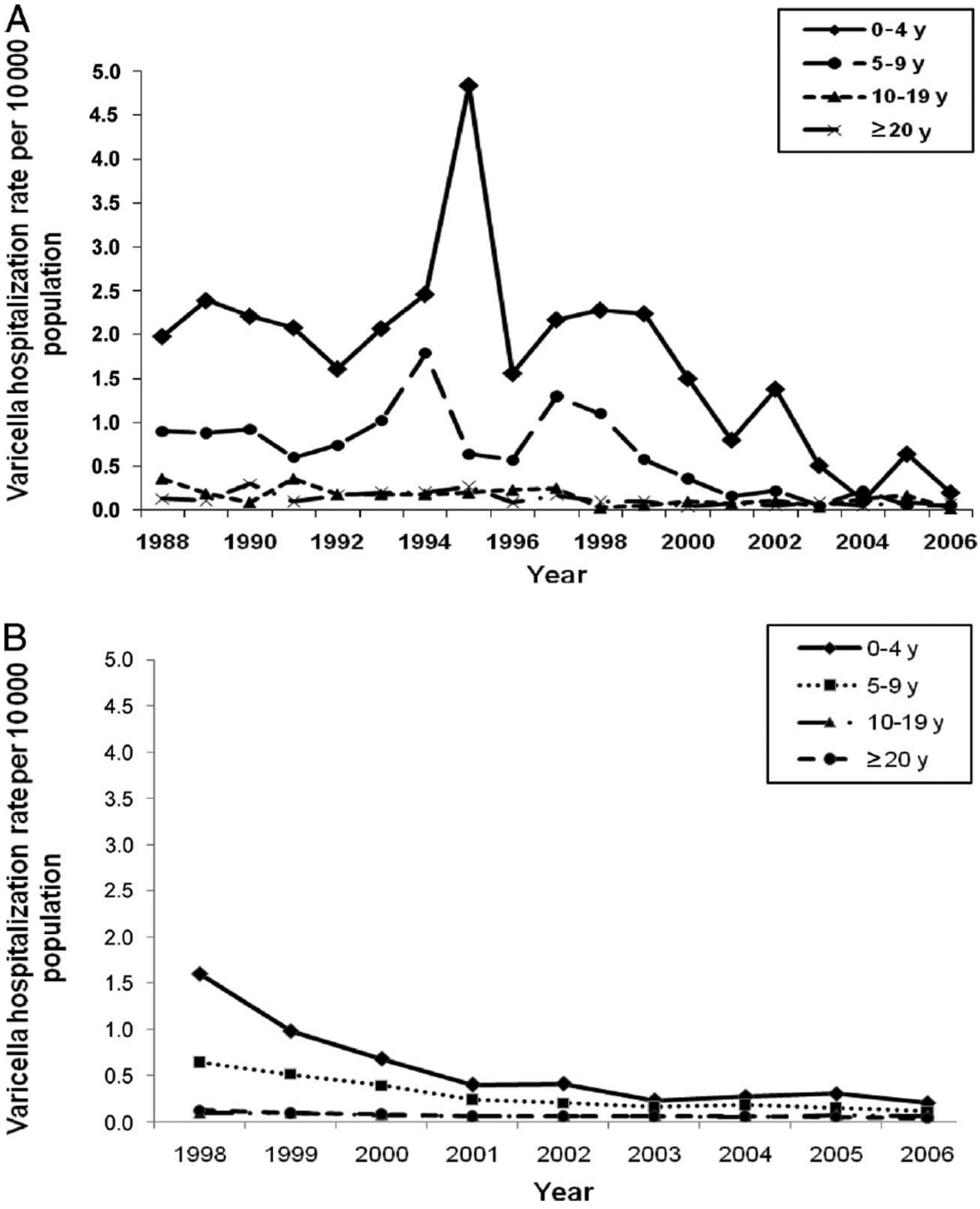

FIGURE 2.

Varicella-related hospitalization rates per 10 000 population according to year and age group. Estimates using the NHDS include data from 1988 to 2006 (A), and estimates using the NIS include data from 1998 to 2006 (B).

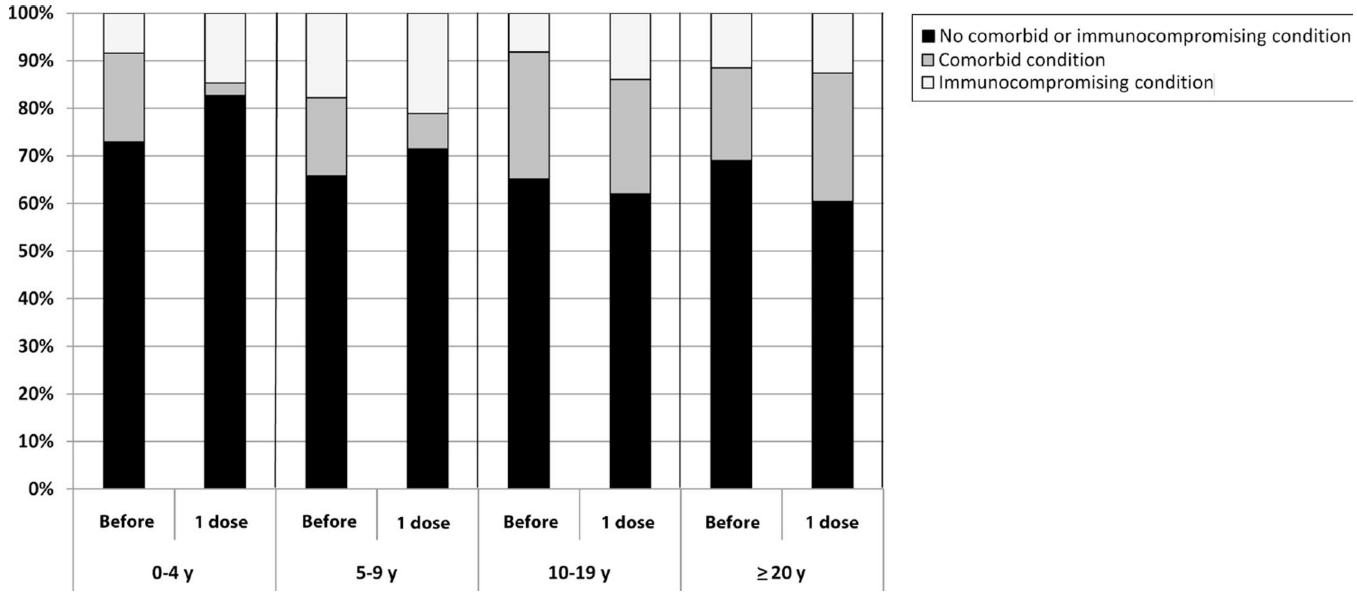

FIGURE 3.

The proportions of varicella-related hospitalizations according to health status and vaccination era (before: prevaccination era; 1 dose: 1-dose vaccination era) for each age group. Proportions were estimated by using data from the NHDS.

TABLE 1

Estimated Numbers and Rates of Varicella-Related Hospitalizations per Year According to Age Group During the Prevaccination (1988–1995) and 1-Dose Vaccination (2000–2006) Eras, United States

Age, y	Total, *n* (%)		Rate per 10 000 Population[a]	
	Prevaccination Era	1-Dose Vaccination Era	Prevaccination Era	1-Dose Vaccination Era
0–4	4724 (44.4)	1376 (39.3)	2.5	0.7
5–9	1731 (16.3)	329 (9.4)	1.0	0.2
10–19	782 (7.4)	386 (11.0)	0.4	0.1
≥20	3394 (31.9)	1407 (40.2)	0.2	0.07
Total	10 632 (100.0)	3498 (100.0)	0.4	0.12

Estimates were calculated by using data from the NHDS.

[a] All differences between the prevaccination and 1-dose vaccination eras were statistically significant ($P < .001$).